Probabilistic hazard characterisation, and integrated probabilistic risk assessment

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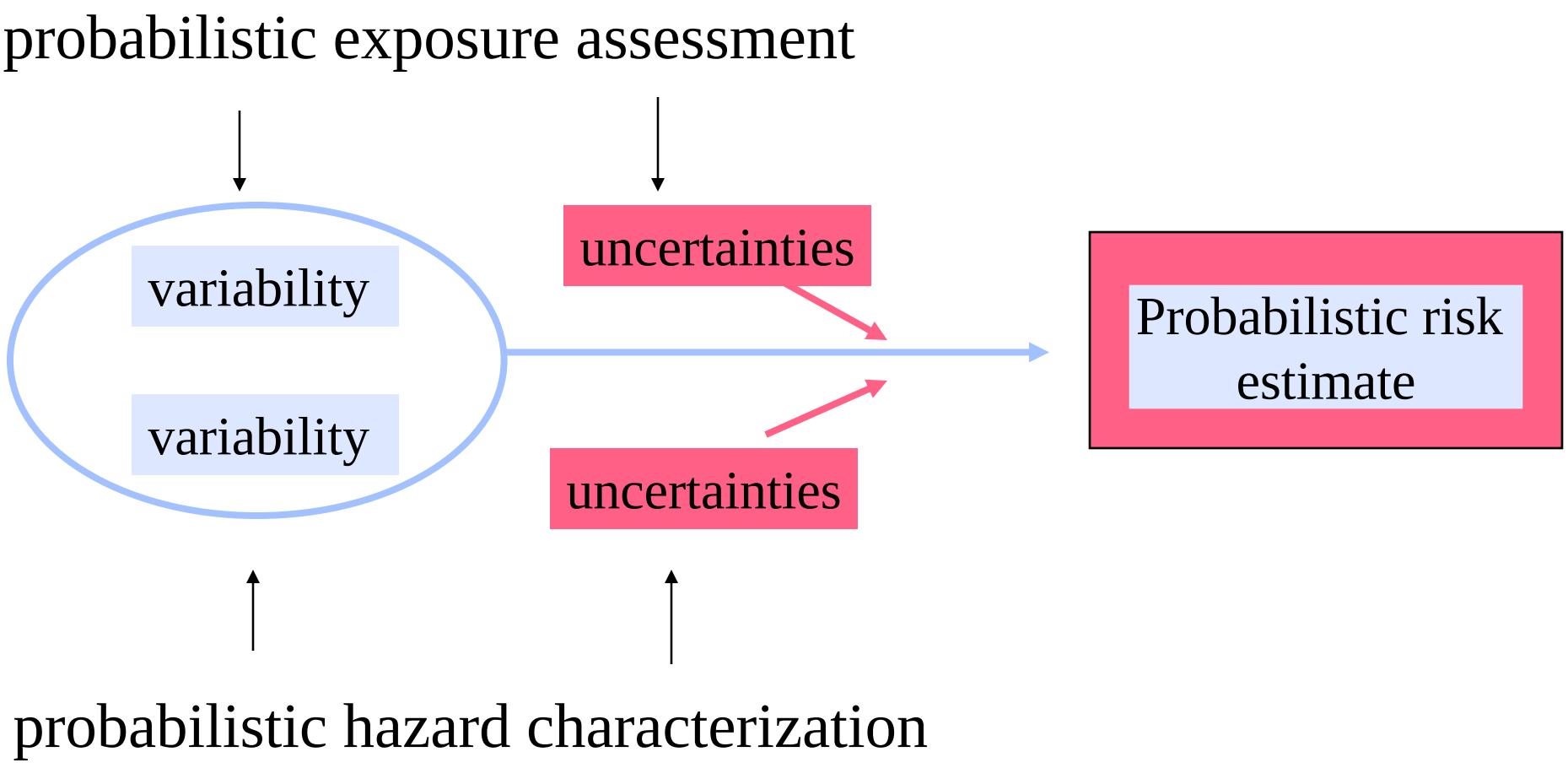
Why Probabilistic Risk Assessment?

- results in less biased risk estimates
- insight in the precision of the risk estimates
- insight in the degree of conservatism (are we really conservative?)
- more adequate comparison of alternative risks / decisions

(integrated) probabilistic risk assessment



Hazard characterization
(deterministic approach)

*uncertainty **not** taken into account*

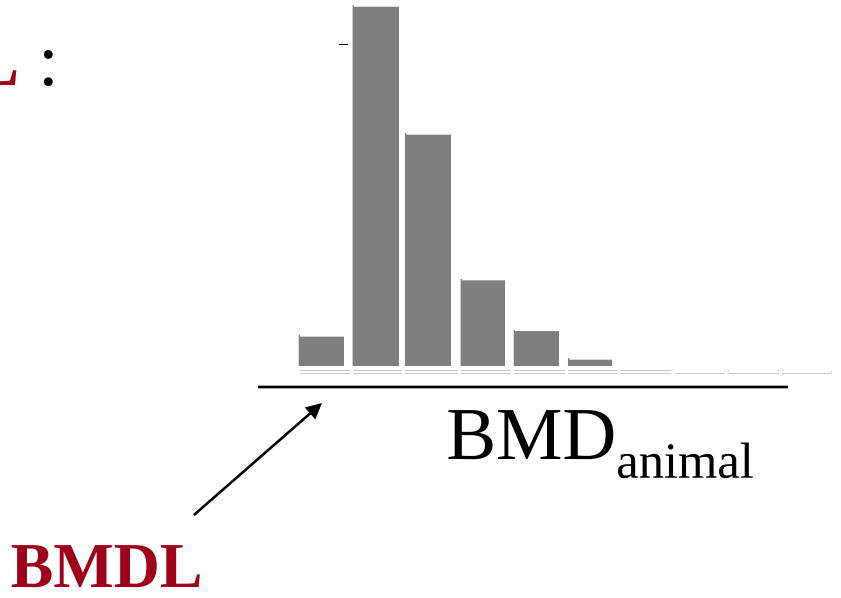
$$RfD = \frac{NOAEL \ \ or \ \ BMDL}{UF_1 \times UF_2 \times UF_3 \times \ldots}$$

uncertainty taken into account
(overdone?)

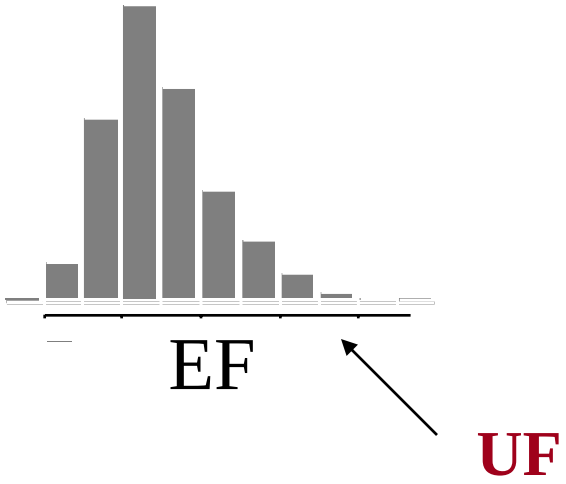
Probabilistic hazard characterisation

- Quantify all the uncertainties
- Give “best” estimate of exposure limit
- Evaluate all uncertainties,
  and give “conservative” estimate of exposure limit

Instead of **NOAEL / BMDL** :

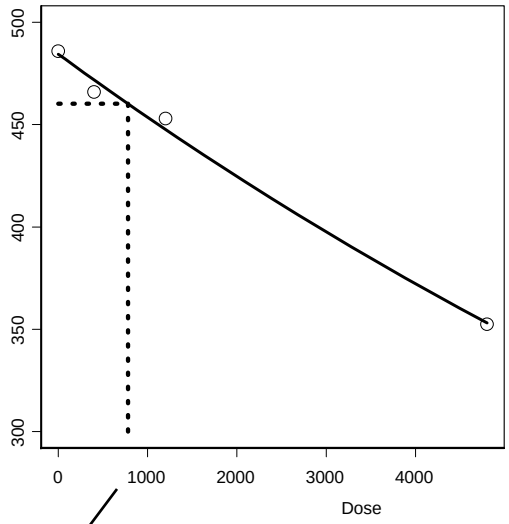


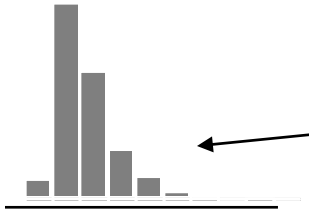
Instead of **UF**:



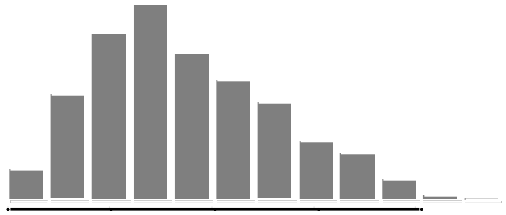
compound-specific experiment

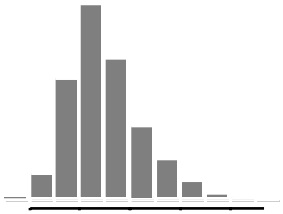
BMR

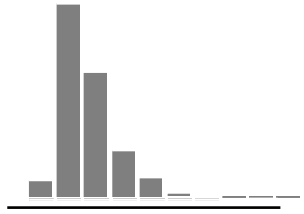




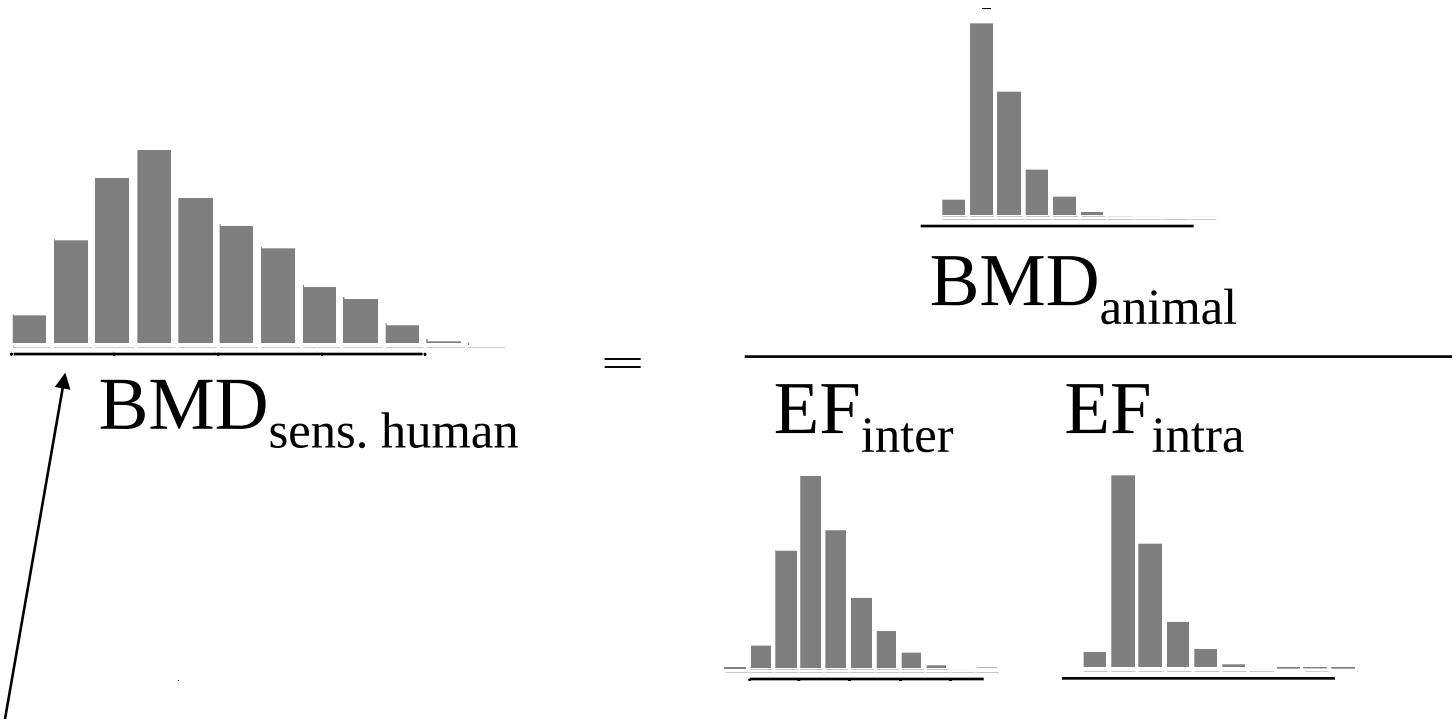
$$BMD_{sens.\ human} = \frac{BMD_{animal}}{EF_{inter} \quad EF_{intra}}$$







historical data



ProbRfD

(e.g., 5th percentile)

UNCERTAINTY !

Slob & Pieters, Risk Anal 1998

What is an EF distribution?
(e.g. interspecies)

Definition

Interspecies difference in sensitivity = ratio of equipotent doses

Assumption

This ratio varies among compounds

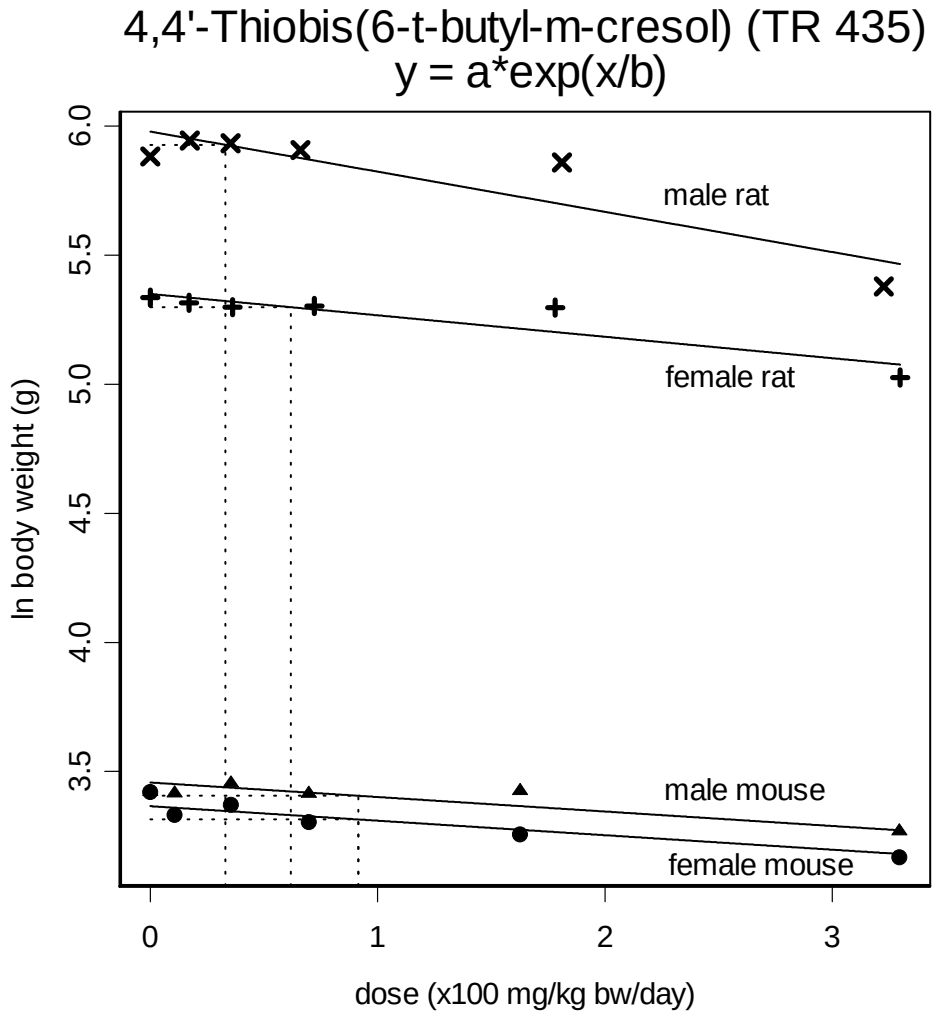
So, $EF_{interspecies} = \frac{BMD_{test\ animal}}{BMD_{average\ human}}$ follows some distribution

Interspecies EF

Recent study : compares rat and mouse by re-evaluation of NTP studies

BMD ratios assessed for 386 data sets

NOAEL ratios assessed for 228 data sets



Interspecies EF

Mouse-to-rat ratios
estimate the EF distribution

		mg/kg	$mg/kg^{0.7}$
NOAEL (n=228)	GM	2.01	1.10
	GSD	3.44	3.43
BMDL (n=368)	GM	1.81	0.99
	GSD	1.98	1.99

assumption

mg/kg is the proper dose scale

rats and mice are (on average) equally sensitive

observation

rats are (on average) more sensitive

$mg/kg^{0.7}$ is the proper dose scale

Interspecies EF

UF $_{\text{interspecies}}$ required to be conservative at the 5% level

	BMDL
Mouse	32
Rat	16
Rabbit	8
Dog	5

Interspecies EF

$UF_{interspecies}$ required to be conservative at the 5% level

	BMDL	NOAEL
Mouse	32	77
Rat	16	38
Rabbit	8	19
Dog	5	13

Bokkers and Slob, CRT, in press

Subchronic-chronic EF

A similar study was done comparing subchronic to chronic :

NOAEL (n=68)	GM	1.5
	GSD	5.3
BMDL (n=189)	GM	1.7
	GSD	2.9

Subchronic-chronic EF

A similar study was done comparing subchronic to chronic :

NOAEL (n=68)	GM	1.5
	GSD	5.3
	P95	23
BMDL (n=189)	GM	1.7
	GSD	2.9
	P95	9.9

Bokkers and Slob, Tox. Sci, 2005

Intraspecies EF

Uncertainty or variability ?

Variation among compounds

Variation among individuals

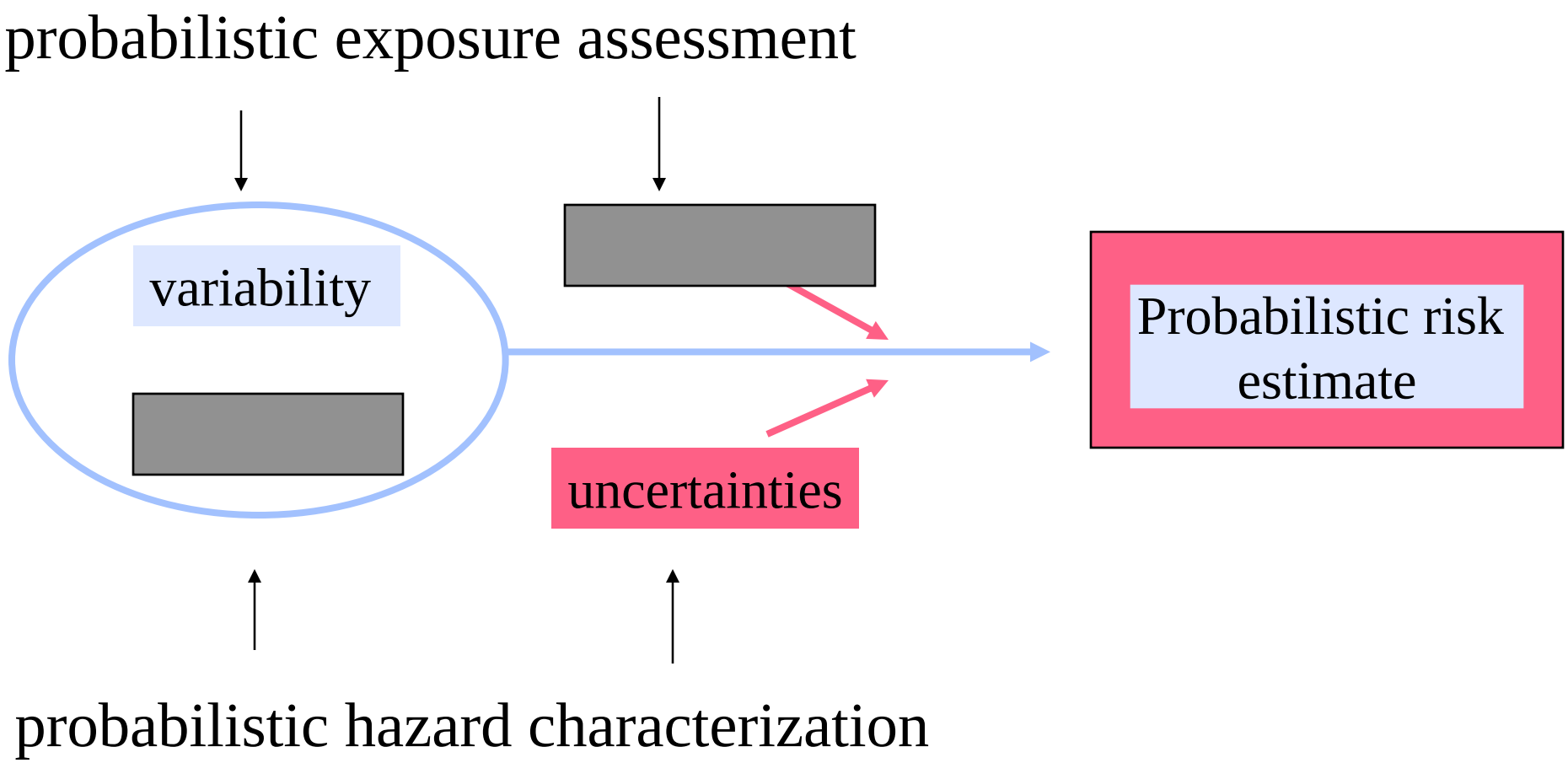
(… plus uncertainty in the data
that may inform the intraspecies factor)

Integrated Probabilistic Risk Assessment

Example 1 (DEHP) : *partly integrated PRA*

Example 2 (acephate) : *fully integrated PRA*

Example 1 (DEHP)



Example 1 (DEHP)

Exposure routes:

- food
- indoor air
- toys (sucking)

Critical effect:

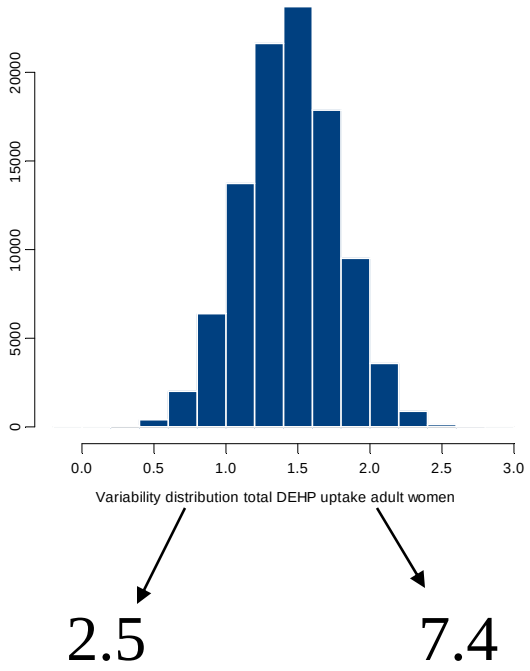
reproductive (testis)

Deterministic approach (RAR):

MOS ~ 100

Example 1 (DEHP)

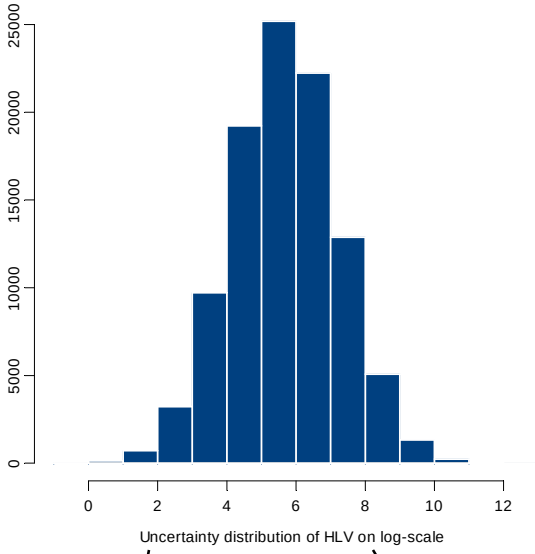
Probablistic exposure assessment



2.5 7.4

Variation in (total) exposure

Probabilistic hazard characterization



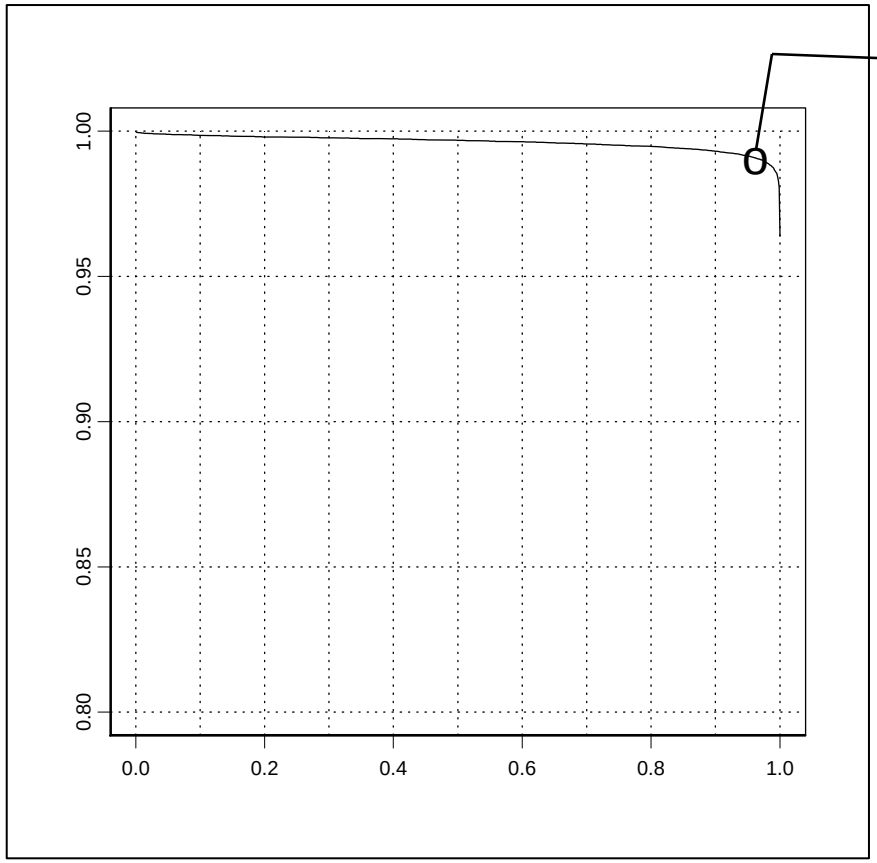
23 3736 ug/kg/d

Uncertainty in $NAEL_{sens.\ human}$

Example 2 (DEHP)

Integrated probabilistic risk characterization

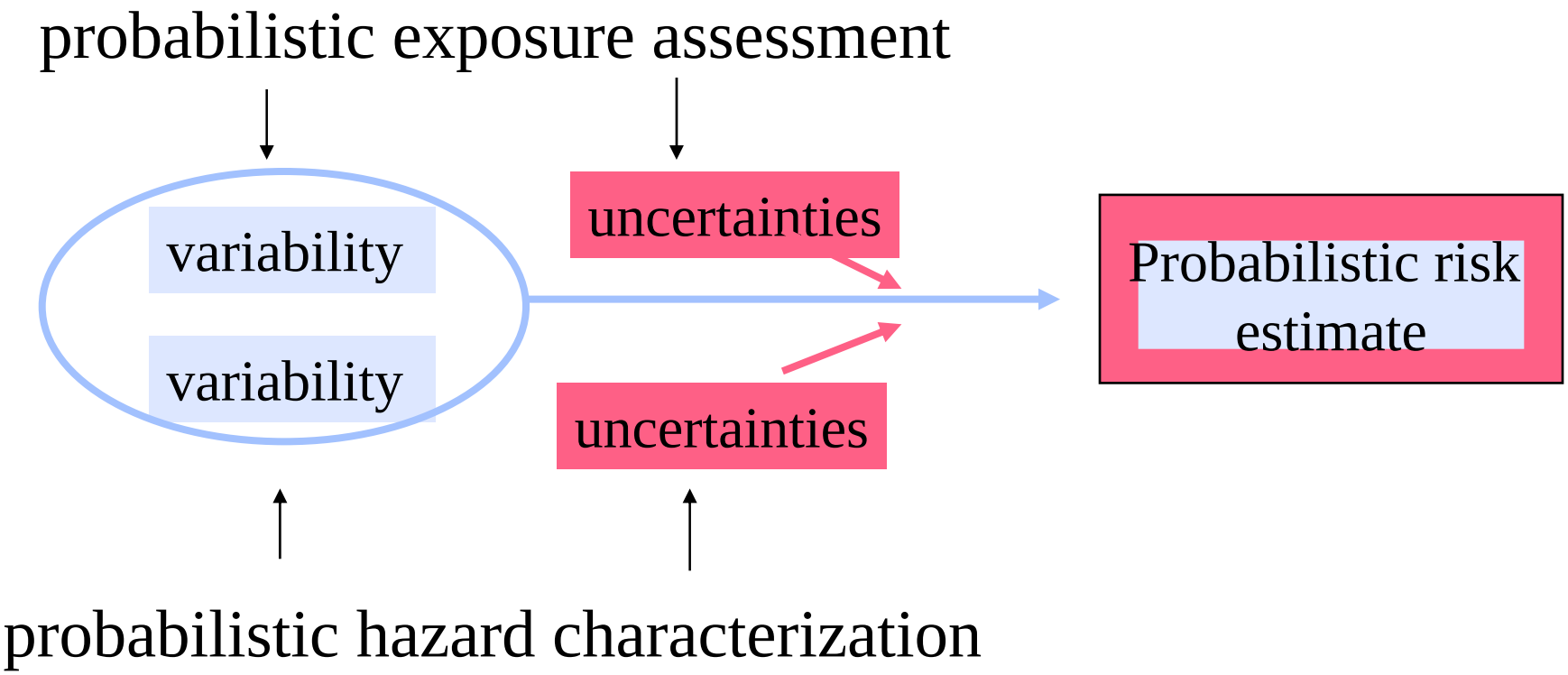
prob.of not exceeding $NAEL_{sens\ hum}$



For 95% of the population exposure is less than NAEL with 99% confidence

Fraction of population

Example 2 (Acephate)



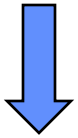
Van der Voet and Slob, Risk Anal, in press

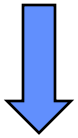
Example 2 (Acephate)

The basic idea

Every person as its own critical-effect dose: ICED distribution

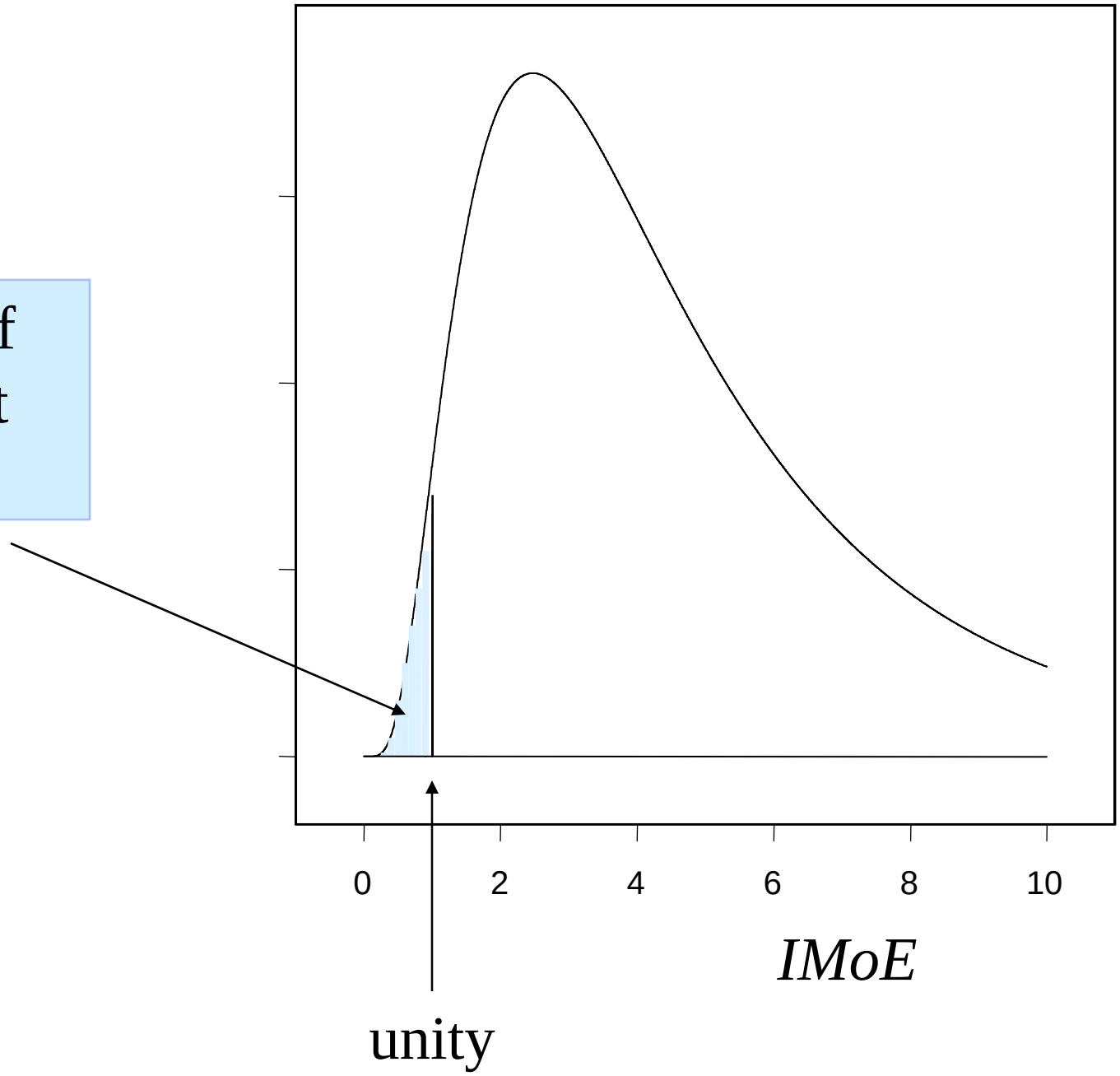
Every person has its own exposure level: IEXP distribution





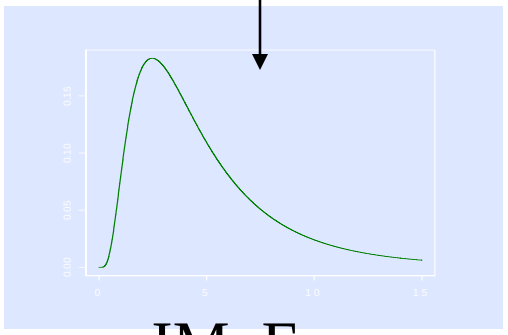
Every person has its own MoE: IMoE distribution

Probability of critical effect PoCE



Integrated PRA, including variability

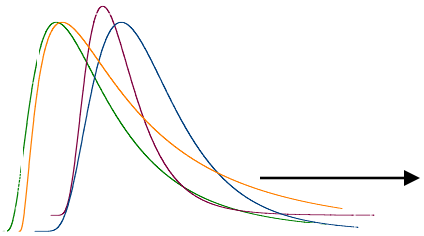
		Variability
EA	Consumption behaviour	yes
EA	Concentrations in food	yes
EA	Food processing	yes
HC	Individual susceptibility	yes
HC	Interspecies extrapolation	no
HC	Animal data	no



IMoE

Integrated PRA, including both uncertainties and variability

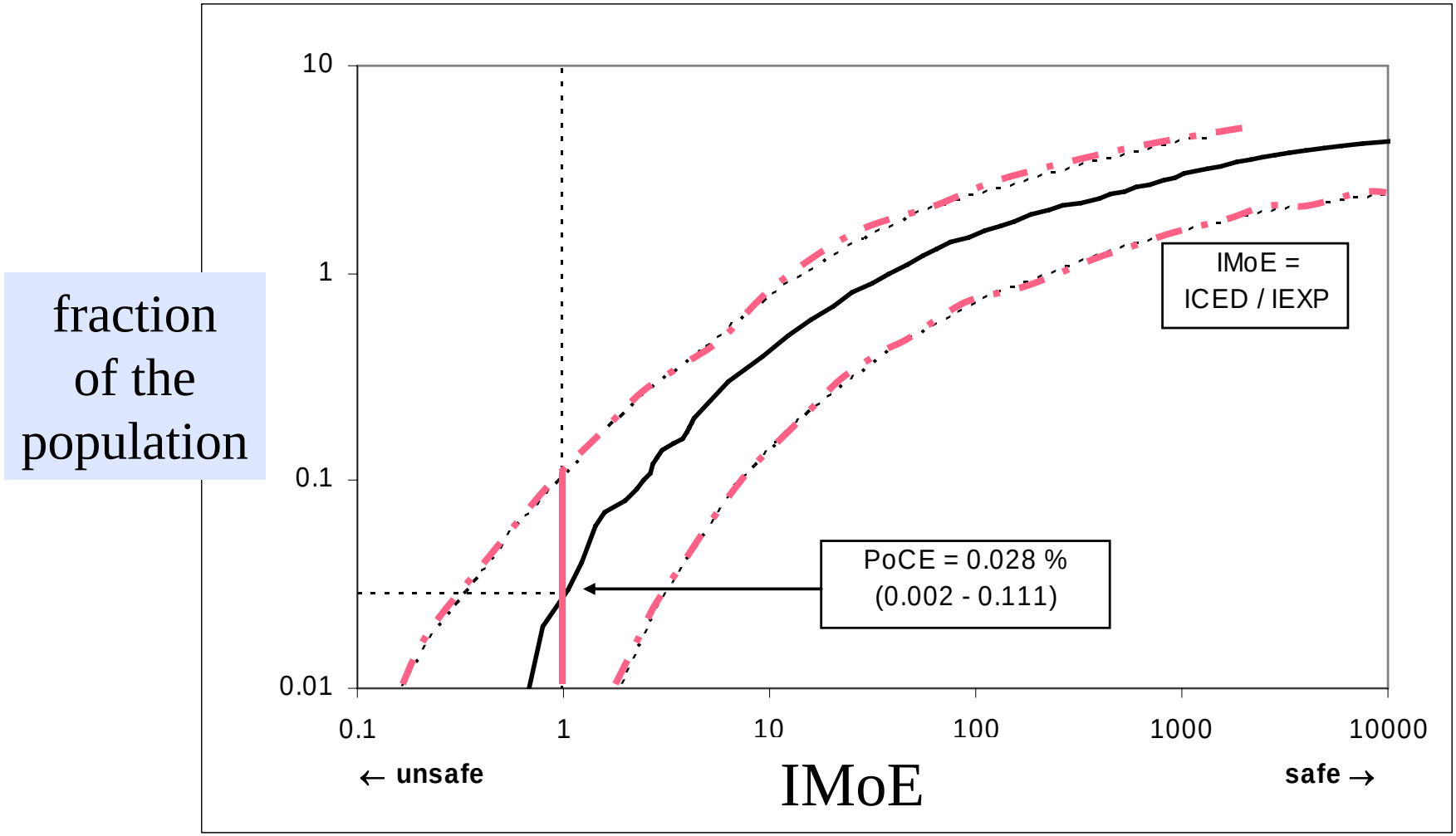
	Variability	Uncertainty
Consumption behaviour	yes	yes
Concentrations	yes	yes
Food processing	yes	yes
Individual susceptibility	yes	yes
Interspecies extrapolation	no	yes
Animal data	no	yes



Plot cumulatively

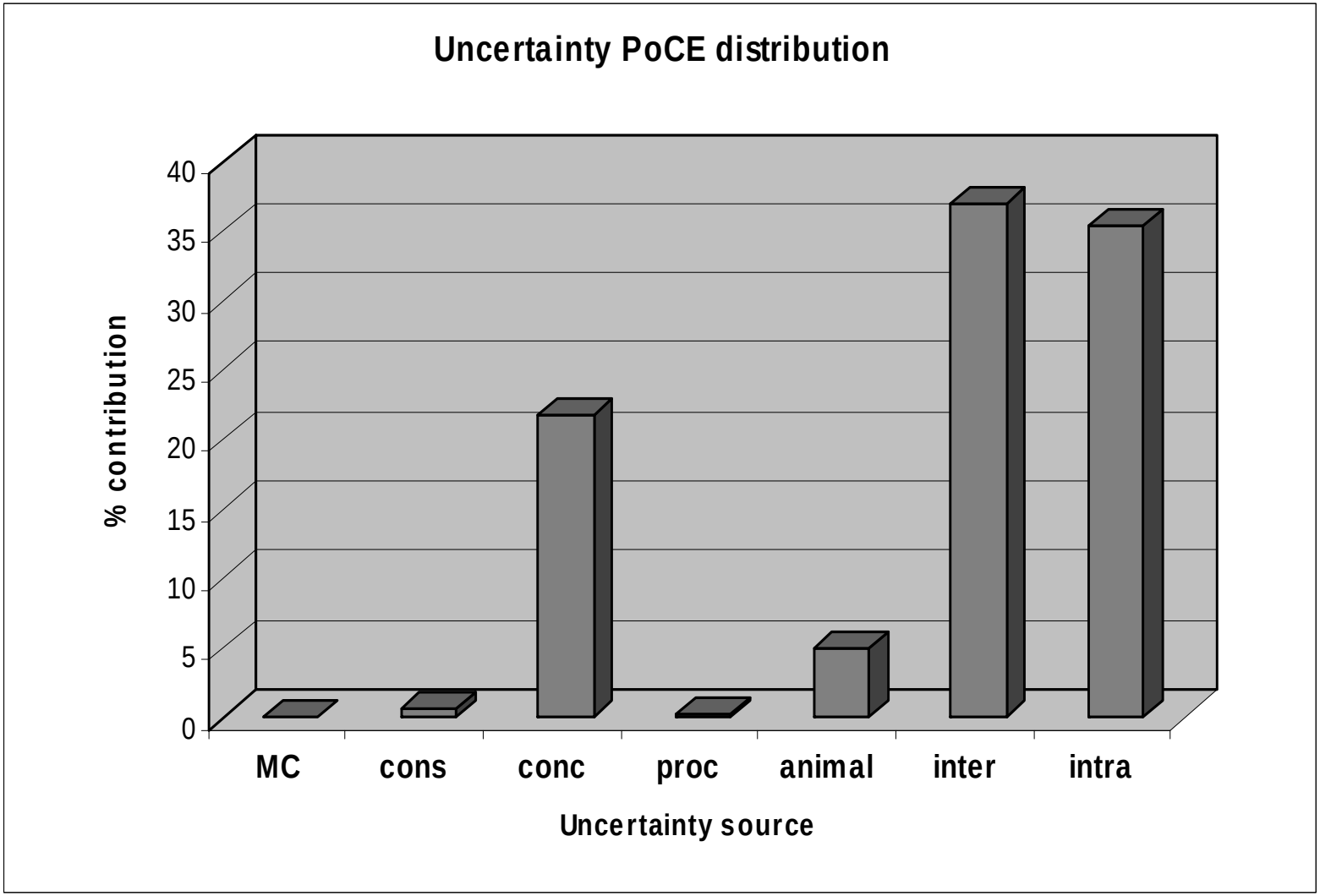
IMoE

Example 2 (Acephate)



(Note: concentrations were multiplied by 100)

Relative contribution of sources of uncertainty



Some conclusions

- PRA results in an estimated **health risk**, and an estimated **risk of being wrong**
- Probabilistic hazard characterization can easily be done in any RA
- Integrated PRA may be done in a tiered approach, e.g. according to the two examples
- The second tier is the most comprehensive and realistic approach, but also more laborious
- Evaluation of relative contribution of uncertainties is very useful

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